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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,768	09/28/2001	Derek Van Der Kooy	Bereskin & Parr	6817

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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,768	VAN DER KOOY ET AL.	
	Examiner	Art Unit	
	Daniel Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 25-46* is/are rejected.

7)☒ Claim(s) *24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office Action is a response to the Application filed September 28, 2001, which claims benefit to U.S. Provisional Application 60/236,394 filed September 29, 2000. Claims 1-46 as originally filed are pending in the application.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 4-9, 33-40 and 43-46 of this application. The following text in the instant Application, which constitutes written description for the indicated claims, was not found in the Provisional Application: page 3, first full paragraph through the second full paragraph; beginning on page 5, final paragraph through line 2 on page 6; beginning the final paragraph on page 6 through the second full paragraph on page 7; page 10, line 18 through page 11, line 3; page 14, the sentence beginning on line 17 through page 17, line 16; EXAMPLE 8 beginning on page 39 through page 10; and the discussion of Example 8 contained within the DISCUSSION OF EXAMPLES 1-8 beginning on page 40. The provisional application does not, therefore, provide adequate written description for the indicated claims and the filing date of the Non-provisional application will be used to determine the patentability of the claims over the teachings found in the prior art.

Specification

The disclosure is objected to because of the following informalities: the disclosure contains several typographical errors (e.g. in the abstract, line 9, gene therapy is misspelled; in the specification page 14, line 32, there appears to be a word missing and the letter "e" is set off by itself; and on page 15, line 16, embryonic is misspelled. Applicant is encouraged to carefully review the disclosure for additional typographical errors.

Appropriate correction is required.

Claim Objections

Claims 9 and 46 objected to because of the following informalities: the claims contain misspelled words (i.e. "neurosphere" in the second line of claim 9 and "said" in the second line of claim 46. Appropriate correction is required.

Claim 14 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be claimed in the alternative. See MPEP § 608.01(n). In the interest of compact prosecution the claim has been interpreted as "The method of claims 1 or 12...".

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-27 and 39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 25-27 are drawn to cells expressing neural precursor cell markers and/or one or more neural-specific mRNA molecules, and having multilineage potential, and claim 39 is drawn to a modulator or differentiation factor. As written,

these claims encompass products of nature and are thus drawn to nonstatutory subject matter. This rejection can be traversed by amending the claims to indicate the hand of man in the invention. For example, by amending the claims to be drawn to isolated cells, modulators or differentiation factors.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 31, 33-35, 37, 38, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 17 is drawn to a method of differentiating one or more pluripotent embryonic stems cells toward one or more neuronal cells wherein the media comprises an inhibitor of TFG-β-related signaling. Given its broadest reasonable interpretation, the inhibitor of the claim encompasses a genus of all compounds capable of inhibiting signaling through the TGF-β receptor and all signaling "related to" signaling through the TGF-β receptor. This genus would comprise diverse set of compounds from antagonists of TGF-β receptor binding, to general inhibitors of kinase and other signaling molecules. The Revised Interim Guidelines state "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "In an unpredictable art, adequate written description of a

genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436). The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). The disclosure provides the BMP antagonists Noggin and Cerberus as the only examples of inhibitors of TGF-β related signaling, and reduces those examples to practice in Example 4. The disclosure does not provide any other examples of inhibitors of TGF-β related signaling that could be added to the medium in accordance with the limitations of the claim. Also, given that Noggin and Cerberus are structurally distinct molecules, the disclosure does not provide the relevant identifying structural characteristics that would confer on a molecule the function of an inhibitor of TGF-β related sequences. In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *any* and *all* inhibitors of TFG-β-related signaling Therefore, only the claims drawn to the described species of inhibitors of TGF-β related signaling meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 31, 33-35, 37, 38, 40 and 41 are drawn to a method of producing a cell type derived from a primitive neural stem cell, a method for screening for modulators of cellular differentiation, or a method for screening for differentiation factors. Given their broadest reasonable interpretation, the claims encompass a method of producing any and all cell types or methods of screening compounds that induce differentiation toward any and all cell types.

However, the disclosure only provides description of the claimed methods as they would be applied to producing or screening for differentiation toward a neural cell phenotype. Given that the methods disclosed could not be used to determine, for example, differentiation toward muscle cell or endothelial cell phenotypes, the Application does not provide adequate written description to support the full scope of the claim. One of ordinary skill in the art would therefore not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate with its scope. Therefore, only the claims drawn to the methods as they are applied to producing or screening for differentiation toward neural cells meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-19, 28, 29 and 37-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of differentiation of embryonic stem cells toward neural cells in serum-free medium and in the absence of a feeder layer, does not reasonably provide enablement for differentiation in the presence of a feeder layer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The relevant art teaches that high cell density inhibits the differentiation of embryonic stem cells toward a neuronal cell type and that embryonic stem cells remain undifferentiated until they are removed from the feeder layer upon which they are commonly grown (see especially Tropepe et

al. (2001) *Neuron* 30: 65-78, page 71 beginning the first full paragraph of column 1 through the first full paragraph of column 2). Given this teaching and the absence of any teachings in the prior art or disclosure as to how embryonic stem cells in culture with a feeder layer could be induced to differentiate toward a neural cell type, considerable empirical research would be required to practice the invention in the presence of a feeder layer. Practicing the invention commensurate with the full scope of the claims would therefore require undue experimentation.

Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein cells are maintained in medium comprising LIF or B27, does not reasonably provide enablement for methods wherein cells are cultured in the absence of LIF or B27. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Tropepe (cited above) teaches that neuronal cell colonies derived from ES cells according to the method of the claimed invention maintain their LIF (B27) dependence upon repeated subcloning (see especially column 1, second full paragraph) and that LIF is "critical for ES-derived neural stem cell colony formation and subsequent stem cell self-renewal". Given this teaching and the absence of any teachings in the prior art or disclosure as to how the method could be used in the absence of LIF or B27, considerable empirical research would be required to devise an alternative method that would allow the skilled artisan to practice the invention without LIF or B27 in the medium. Practicing the invention commensurate with the full scope of the claims would therefore require undue experimentation.

Claims 44-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to methods of treating neurodegenerative disorders or neural diseases or conditions comprising administering the cells of claim 29, or a genetically modified descendent of said cells, to a patient in need thereof.

In view of the level of skill and the state of the art at the time of the effective filing date, the level of unpredictability in the art is extremely high. This state is properly illustrated by recently published art such as Donovan and Gearhart (*Nature* (2001) 414: 92-97), which teaches "So far, there have been few demonstrations that derivatives of stem cells can be transplanted successfully in animal models of diseases or injuries, but the demonstration is remarkable", "If stem cells are to be used to treat a wide variety of human diseases, then we will need to overcome several formidable challenges. Stem cells will be needed in large quantities and be able to differentiated in a controlled manner to form homogeneous populations of cells that are histocompatible with an individual" (left column on page 95). Weissman (*Science* (2000) 287:1442-1446) teaches that although clinical stem cell transplantation could greatly add to the physician's armamentarium against degenerative diseases, there are still long way to go in reality. The barriers are the complicated immunological responses from the host to the transplanted cells, and the state of primary diseases of these patients (see the entire article). The take-home message is "It is reasonable to expect that cotransplantation of HSCs and tissue or organ stem and progenitor cells will occur increasingly over the next two decades and will result from the intersecting advances in stem cell biology and stem/tissue transplant immunology".

Furthermore, at the time of the filing date, one still cannot extrapolate results from *ex vivo* studies or studies generated in laboratory animals to human therapy. Donovan and Gearhart

teach "Human stem cell populations proliferate more slowly than their murine counterparts, differentiate more readily and their cloning efficiency is very low" (last paragraph on page 95), "Only time will tell whether the results of cell transplantation in animal models can be recapitulated in humans and whether it will prove impossible to make certain cell types from pluripotent stem cells" (last paragraph on page 96). Accordingly, in view of the quantity of experimentation necessary to achieve a therapeutic treatment of neurodegenerative disorders or diseases or conditions of the neural system stem cells, the lack of guidance provided by the specification, the absence of working examples with regard to therapy of neural diseases, and the breadth of the claim directed to the use of neural stem cells in patients, it would required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method wherein the media comprises an inhibitor of TGF-β-related signaling. The metes and bounds of the claims are unclear because the disclosure does not define in what way these signaling pathways must be related to TGF-β. For example, must they be activated or inhibited as a direct consequence of receptor activation or does this include signaling pathways that are not directly coupled to TGF-β receptor activation but intersect TGF-β signaling such as in cross-talk regulation of one receptor by another. This rejection can be

traversed by amending claim 17 so that the claims are drawn to inhibitors of TGF-β signal transduction; however, as argued above, the specification provides adequate written description only for the inhibitors identified in the disclosure.

Claim 19 is also indefinite because it is drawn to the "Cerebus" family of proteins, which are not described in the specification. The claim has been examined with the assumption that Applicant intends the claim to be drawn the Cerberus proteins described in the specification. In addition, claim 19 is indefinite because it depends from claim 18, which is drawn to the protein Noggin and not a genus comprising the Cerberus family of proteins. It would appear that applicant intended that the claim depend from claim 17 and, in the interest of compact prosecution, the claim has been examined on the merits with that assumption.

Claim 36, which depends from claim 35, refers to the limitation "modulators" in the first line. There is insufficient antecedent basis for this limitation in the claim 35 which is drawn to a method for screening for differentiation factors.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 4 and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by Tropepe et al. (April 2001) *Neuron* 30: 65-78.

The claims are drawn to a method for differentiating one or more pluripotent ES cells toward one or more neural cells wherein the cell density is greater than 0 cells/μl to 50 cells/μl or greater than 0 cells/μl to 20 cells/μl. Please note that, for the reasons cited above, the priority

date for these claims is September 28, 2001, and that because the cited reference lists authors that are not named as inventors on the instant application, the reference is considered prior art under 35 USC § 102(a). Tropepe (2001) teaches a method for differentiating pluripotent ES cells wherein the cell density is 20 cells/μl. The teachings of Tropepe are the same as those of the instant application, therefore the limitations of the claims are anticipated by Tropepe.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25, 26, 29-31 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Fraichard et al (1995) *J. Cell Sci.* 108:3181

Claim 25 is drawn to one or more cells expressing one or more neural precursor cell marker(s) and/or one or more neural-specific mRNA molecules and having multilineage potential. Claim 26 limits the neural precursor marker of claim 25 to nestin. Claim 29 is drawn to a primitive neural stem cell produced by the method of claim 12 that comprises neural cell markers and is pluripotent. Please note that claim 29 is drawn to a product by process. Although Applicant asserts that the primitive neural stem cells of the invention are unique in that they have a much greater degree of pluripotential fates than do the definitive neural stem cells obtained by other means (page 15, lines 21-24), no evidence is provided to support this claim. Also, it is not possible to argue that the primitive neural stem cells cited here as prior art are different from the cells of the instant application without a direct side by side comparison because the authors do not present an exhaustive analysis of all potential fates for the described cells. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) states: "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the

product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." For these reasons the claim is interpreted to read on a primitive neural stem cell produced by any means.

Claim 30 is drawn to a neural stem cell comprising at least one neural cell marker and is pluripotent. Claim 31 is drawn to a method of producing a pre-selected cell type derived from the cell of claim 30 comprising, culturing the cells under differentiating conditions that promote formation of the cell type.

Fraichard teaches cells expressing the neural precursor marker nestin (see especially **Antigenic characterization of neuron-glia precursors** beginning on page 3183, column 2 and continuing through the second line on page 3184, and Figure 3 and the caption thereto) and goes on to teach that these cells have multilineage potential (see **Antigenic characterization of glial cells** and **Antigenic characterization of neurons** on pages 3184 and 3185 respectively) by culturing the cells under conditions that lead to their differentiation into post mitotic neurons and glial cells (see especially **Experimental procedure** beginning on page 3182, column 1 and continuing through page 3183, first paragraph).

Claim 39 is also a product by process claim drawn to a modulator or differentiation factor. Accordingly the retinoic acid used by Fraichard to induce differentiation reads on the claim.

The cells, method and differentiation factor taught by Fraichard are the same as those taught in the instant application, therefore the limitations of the claims are met by Fraichard.

Claims 25, 26 and 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Okabe et al. (1996) *Mechanisms of Development* 59: 89-102.

The limitations of claims 25, 26 and 29-32 are recited above. Claim 32 is drawn to the method of claim 31 wherein the cell type is a neural cell and the differentiating conditions comprise culturing the cell in a serum free medium that comprises FGF2.

Okabe teaches neural stem cells expressing the neural precursor marker nestin (see especially page 90, column 1, approximately half way down the first full paragraph and Figure 1 and the caption thereto), and that the cells have multilineage potential by culturing the cells under conditions that lead to their differentiation into post mitotic neurons and glial cells. (see 2.3 *Differentiation of neuronal precursor cells toward neuronal and glial lineages* beginning on page 92, column 1 and continuing through the first paragraph on page 93). Okabe also teaches production of a proliferating nestin-positive neuronal cell in serum-free medium supplemented with bFGF (known in the art to be synonymous with FGF2; see section 2.2 *Proliferation of neuronal precursor cells in the presence of bFGF* beginning on page 90 column 2).

The cells and method of Okabe are the same as those taught in the instant application, therefore the claim limitations are anticipated by Okabe.

Claims 33-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Tropepe et al (1999) *Soc. Neurosci. Abstracts* 25: 527.

Claim 33 is drawn to a method for screening for modulators of cellular differentiation comprising culturing pluripotent cells in serum-free media at low density in the presence of a

potential modulator, allowing for differentiation and detecting differentiated cell types. Claim 34 is drawn to the method of claim 33 wherein the modulators comprise any culturing conditions that may modulate differentiation. Claim 35 is drawn to a method of screening for differentiation factors comprising culturing cells in serum free medium at low cell density in the presence of a differentiation factor, allowing for differentiation and detecting differentiation. Claim 36 limits the method of claim 35 to a method for screening for differentiation factors of neural cell development. Claim 37 is drawn to a method for screening for differentiation factors comprising culturing the cells of claim 29 in serum free media in the presence of a differentiation factor and detecting differentiation of the cell. Claim 38 is drawn to the method of claim 37 wherein the media further comprises FGF2 and claim 40 is drawn to the method of claim 38 for modulating cellular differentiation.

As indicated above, the priority date for these claims is September 28, 2001. Tropepe (1999) teaches a method for screening for modulators or differentiation factors of neural cell development comprising culturing the cells made according to the instant invention in the presence of a FGF2 and a modulator or differentiation factor (i.e. Noggin), allowing cells to differentiate and detecting differentiation indicating that the method of Tropepe (1999) is a method for modulating cellular differentiation.

Claim 39 is drawn to a modulator or differentiation factor detected by the methods of claims 33-37. Accordingly, Noggin reads on the claim.

The methods and differentiation factor taught by Tropepe (1999) are the same as those taught in the instant application, therefore the limitations of the claims are met by Tropepe (1999).

Allowable Subject Matter

Claim 24 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
August 16, 2002

JAMES KETTER
PRIMARY EXAMINER